

We claim:

1. A method for identifying bioactivities or biomolecules using high throughput screening of nucleic acid comprising:
 - a) providing a gene library containing a plurality of clones, wherein the DNA for generating the library is obtained from more than one organism;
 - b) encapsulating a bioactive substrate and at least one clone of the library in a gel microdroplet, wherein a bioactivity or biomolecule produced by the clone is detectable by a difference in the substrate prior to contacting with the at least one clone as compared to after contacting;
 - c) screening the microdroplet with an assay or an analyzer that detects a bioactivity or biomolecule; and
 - d) identifying clones detected as positive for a change in the substrate, wherein a change in the substrate is indicative of DNA that encodes a bioactivity or biomolecule.
2. The method of claim 1, wherein the bioactivity is provided by an enzyme is selected from the group consisting of lipases, esterases, proteases, glycosidases, glycosyl transferases, phosphatases, kinases, mono- and dioxygenases, haloperoxidases, lignin peroxidases, diarylpropane peroxidases, epoxide hydrolases, nitrile hydratases, nitrilases, transaminases, amidases, and acylases.
3. The method of claim 1, wherein the library is generated in a prokaryotic cell.
4. The method of claim 1, wherein the library is generated in a *Streptomyces* sp.
5. The method of claim 4, wherein the *Streptomyces* is *Streptomyces venezuelae*.
6. The method of claim 3, wherein the prokaryotic cell is gram negative.
7. The method of claim 1, wherein the gene library is an expression library.

8. The method of claim 5, wherein the expression library contains DNA obtained from extremophiles.
9. The method of claim 8, wherein the extremophiles are thermophiles.
10. The method of claim 9, wherein the extremeophiles are selected from the group consisting of hyperthermophiles, psychrophiles, halophiles, psychrotrophs, alkalophiles, and acidophiles.
11. The method of claim 1, wherein the bioactive substrate comprises C12FDG.
12. The method of claim 1, wherein the bioactive substrate comprises a lipophilic tail.
13. The method of claim 1, wherein the samples are heated before step b).
14. The method of claim 13, wherein the heating is at about 70°C.
15. The method of claim 14, wherein the heating occurs at about 30 minutes.
16. The method of claim 1, wherein the analyzer comprises a fluorescent analyzer.
17. The method of claim 16, wherein the fluorescent analyzer is a FACS apparatus.
18. The method of claim 1, wherein the library is biopanned before step b).
19. The method of claim 4, wherein the prokaryotic cell is *E. coli*.
20. The method of claim 19, wherein prior to step b), the *E. coli* is transferred to a *Streptomyces* sp.

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21. The method of claim 20, wherein the *Streptomyces* sp. is *Streptomyces venezuelae*.
 22. The method of claim 1, wherein the library is normalized before step b).
 23. The method of claim 1, further comprising co-encapsulating an indicator cell in step b).
 24. The method of claim 1, wherein the analyzer is a chromogenic analyzer.
 25. The method of claim 1, wherein the assay is an immunoassay.
 26. A method for identifying bioactivities or biomolecules using high throughput screening of nucleic acid comprising:
 - a) providing a gene library containing a plurality of clones, wherein the nucleic acid for generating the library is obtained from more than one organism;
 - b) inserting a bioactive substrate into the clones of the library, wherein a change in the substrate is detectable in the presence of a bioactivity or biomolecule;
 - c) screening the clones with an assay or an analyzer that detects the presence of a bioactivity or a biomolecule; and
 - d) identifying clones detected as positive for a change in the substrate, wherein a change in the substrate is indicative of DNA that encodes a bioactivity or biomolecule.
 27. The method of claim 26, further comprising encapsulation the clone and the bioactive substrate prior to screening.

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28. The method of claim 27, wherein the bioactivity is provided by an enzyme is selected from the group consisting of lipases, esterases, proteases, glycosidases, glycosyl transferases, phosphatases, kinases, mono- and dioxygenases, haloperoxidases, lignin peroxidases, diarylpropane peroxidases, epoxide hydrolases, nitrile hydratases, nitrilases, transaminases, amidases, and acylases.
29. The method of claim 27, wherein the library is generated in a prokaryotic cell.
30. The method of claim 27, wherein the library is generated in a *Streptomyces* sp.
31. The method of claim 30, wherein the *Streptomyces* is *Streptomyces venezuelae*.
32. The method of claim 29, wherein the prokaryotic cell is gram negative.
33. The method of claim 27, wherein the gene library is an expression library.
34. The method of claim 31, wherein the expression library contains DNA obtained from extremophiles.
35. The method of claim 34, wherein the extremophiles are thermophiles.
36. The method of claim 35, wherein the extremeophiles are selected from the group consisting of hyperthermophiles, psychrophiles, halophiles, psychrotrophs, alkalophiles, and acidophiles.
37. The method of claim 27, wherein the bioactive substrate comprises C12FDG.
38. The method of claim 27, wherein the bioactive substrate comprises a lipophilic tail.

39. The method of claim 27, wherein the the samples are heated before step b).
40. The method of claim 39, wherein the heating is at about 70°C.
41. The method of claim 40, wherein the heating occurs at about 30 minutes.
42. The method of claim 27, wherein the analyzer comprises a fluorescent analyzer.
43. The method of claim 42, wherein the fluorescent analyzer is a FACS apparatus.
44. The method of claim 27, wherein the library is biopanned before step b).
45. The method of claim 29, wherein the prokaryotic cell is *E. coli*.
46. The method of claim 45, wherein prior to step b), the *E. coli* is transferred to a myceliate bacteria or fungi.
47. The method of claim 46, wherein the myceliate fungi is an *Actinomyces* sp.
48. The method of claim 46, wherein the myceliate bacteria is a *Streptomyces* sp.
49. The method of claim 47, wherein the *Streptomyces* sp. is *Streptomyces venezuelae*.
50. The method of claim 27, wherein the library is normalized before step b).
51. The method of claim 27, further comprising co-encapsulating an indicator cell in step b).
52. The method of claim 27, wherein the analyzer is a chromogenic analyzer.

53. The method of claim 27, wherein the assay is an immunoassay.

54. A method of screening for an agent that modulates the activity of a target cell component, wherein the target cell component and a selectable marker are expressed by a cell, the method comprising co-encapsulating the agent in a microenvironment with the recombinant cell expressing the target cell component and detectable marker and detecting the effect of the agent on the activity of the cell component.

55. The method of claim 54, wherein the agent is an enzyme or small molecule.

56. The method of claim 54, wherein the agent is derived from a gene expression library.

57. The method of claim 55, wherein the enzyme is selected from the group consisting of lipases, esterases, proteases, glycosidases, glycosyl transferases, phosphatases, kinases, mono- and dioxygenases, haloperoxidases, lignin peroxidases, diarylpropane peroxidases, epoxide hydrolases, nitrile hydratases, nitrilases, transaminases, amidases, and acylases.

58. The method of claim 54, wherein the agent inhibits the activity of the target cell component.

59. The method of claim 54, wherein the agent enhances the activity of the target cell component.

60. The method of claim 54, wherein the agent is expressed from a recombinant cell co-encapsulated with the recombinant cell expressing the target cell component and detectable marker.

61. The method of claim 54, wherein the cell is a ~~eukaryotic~~ cell.
62. The method of claim 54, wherein the cell is a prokaryotic cell.
- Sub 44
63. The method of claim 54, wherein the micro-environment is a liposome, gel microdrop, bead, agarose, ~~cell~~, or ghost cell.
64. The method of claim 63, wherein the liposomes are prepared from one or more phospholipids, glycolipids, steroids, alkyl phosphates or fatty acid esters.
65. The method of claim 64, wherein the phospholipids are selected from the group consisting of lecithin, sphingomyelin and dipalmitoyl.
66. The method of claim 64, wherein the steroids are selected from the group consisting of cholesterol, cholestanol and lanosterol.
- Sub 803
67. The method of claim 54, wherein the detectable marker is a fluorescent dye, a visible dye, a bioluminescent molecule, a chemiluminescent molecule, a radioactive material, or an enzymatic substrate.
68. The method of claim 67, wherein the bioluminescent material is green fluorescent protein (GFP) or red fluorescent protein (RFP).
- Sub 13
69. The method of claim 67, wherein detection of the fluorescent dye or a visible dye is carried out by fluorometric or spectrophotometric measurement.
- Sub 13
70. The method of claim 54, wherein the protein is a transducing protein.
71. The method of claim 70, wherein the transducing protein is a G-protein.

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72. The method of claim 54, wherein the recombinant cell is a eukaryotic cell.
73. The method of claim 54, wherein the recombinant cell is a prokaryotic cell.
74. A method for enriching for target DNA sequences containing at least a partial coding region for at least one specified activity in a DNA sample comprising:
- a) co-encapsulating in a micro-environment a mixture of target DNA obtained from more than one organism with a mixture of DNA probes comprising a detectable marker and at least a portion of a DNA sequence encoding at least one enzyme having a specified enzyme activity;
 - b) incubating the co-encapsulated mixture under such conditions and for such time as to allow hybridization of complementary sequences; and
 - c) screening for the specified activity.
75. The method of claim 74, further comprising transforming host cells with recovered target DNA to produce an expression library of a plurality of clones.
76. The method of claim 74, wherein the organisms are microorganisms.
77. The method of claim 76, wherein the microorganisms are uncultured microorganisms.
78. The method of claim 74, further comprising screening the expression library for the specified enzyme activity.

79. The method of claim 74, wherein the target DNA obtained from the DNA population is selected by:
- a) converting double stranded DNA into single stranded DNA;
 - b) recovering from the converted single stranded DNA, single stranded target DNA which hybridizes to probe DNA;
 - c) converting recovered single stranded target DNA to double stranded DNA; and
 - e) transforming a host cell with the double stranded DNA of c).
80. The method of claim 72, wherein screening is by FACS analysis.
81. The method of claim 74, wherein said target DNA is gene cluster DNA.
82. The method of claim 77, wherein the uncultured microorganisms are derived from an environmental sample.
83. The method of claim 77, wherein the uncultured microorganisms comprise a mixture of terrestrial microorganisms or marine microorganisms or airborne microorganisms, or a mixture of terrestrial microorganisms, marine microorganisms and airborne microorganisms.
84. The method of claim 75, wherein the clones comprise a construct selected from the group consisting of phage, plasmids, phagemids, cosmids, fosmids, viral vectors, and artificial chromosomes.
85. The method of claim 74, wherein the target DNA comprises one or more operons, or portions thereof, of the DNA population.

86. The method of claim 85, wherein the operon or portions thereof encodes a complete or partial metabolic pathway.
87. The method of claim 77, wherein the uncultured microorganisms comprise extremophiles.
88. The method of claim 87, wherein the extremophiles are selected from the group consisting of thermophiles, hyperthermophiles, psychrophiles, barophiles, and psychrotrophs.
89. The method of claim 79, wherein the host cell is selected from the group consisting of a bacterium, fungus, plant cell, insect cell and animal cell.
90. The method of claim 74, wherein the target DNA encodes a protein.
91. The method of claim 90, wherein the protein is an enzyme.
92. The method of claim 91, wherein the enzyme is selected from the group consisting of oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases.
93. The method of claim 74, wherein the micro-environment is a liposome, gel microdrop, bead, agarose, cell, ghost red blood cell or ghost macrophage.
94. The method of claim 93, wherein the liposomes are prepared from one or more phospholipids, glycolipids, steroids, alkyl phosphates or fatty acid esters.
95. The method of claim 94, wherein the phospholipids are selected from the group consisting of lecithin, sphingomyelin and dipalmitoyl.

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96. The method of claim 94, wherein the steroids are selected from the group consisting of cholesterol, cholestanol and lanosterol.
 97. The method of claim 74, wherein the detectable marker is a fluorescent dye, a visible dye, a bioluminescent material, a chemiluminescent material, a radioactive material, or an enzymatic substrate.
 98. The method of claim 97, wherein the bioluminescent material is green fluorescent protein (GFP) or red fluorescent protein (RFP).
 99. The method of claim 98, wherein detection of the fluorescent dye or a visible dye is carried out by fluorometric or spectrophotometric measurement.
 100. A method of screening for an agent that modulates the interaction of a first test protein linked to a DNA binding moiety and a second test protein linked to a transcriptional activation moiety, comprising co-encapsulating the agent with the first test protein and second test protein in a suitable microenvironment and determining the ability of the agent to modulate the interaction of the first test protein linked to a DNA binding moiety with the second test protein covalently linked to a transcriptional activation moiety, wherein the agent enhances or inhibits the expression of a detectable protein, and wherein the enhancement or inhibition is detected by FACS analysis.
 101. The method of claim 100, wherein the agent is an enzyme or small molecule.
 102. The method of claim 101, wherein the enzyme is selected from the group consisting of lipases, esterases, proteases, glycosidases, glycosyl transferases, phosphatases, kinases, mono- and dioxygenases, haloperoxidases, lignin peroxidases, diarylpropane peroxidases, epoxide hydrolases, nitrile hydratases, nitrilases, transaminases, amidases, and acylases.

103. The method of claim 100, wherein the agent inhibits the activity of the first protein or the second protein.
104. The method of claim 100, wherein the agent enhances the activity of the first protein or the second protein.
105. The method of claim 100, wherein the agent is expressed from a recombinant cell co-encapsulated with the recombinant cell expressing the target protein and detectable marker.
106. The method of claim 105, wherein the recombinant cell is a eukaryotic cell.
107. The method of claim 105, wherein the recombinant cell is a prokaryotic cell.
108. The method of claim 100, wherein the micro-environment is a liposome, gel microdrop, bead, agarose, cell, ghost red blood cell or ghost macrophage.
109. The method of claim 108, wherein the liposomes are prepared from one or more phospholipids, glycolipids, steroids, alkyl phosphates or fatty acid esters.
110. The method of claim 109, wherein the phospholipids are selected from the group consisting of lecithin, sphingomyelin and dipalmitoyl.
111. The method of claim 109, wherein the steroids are selected from the group consisting of cholesterol, chlorestanol and lanosterol.
112. The method of claim 100, wherein the detectable marker is a fluorescent dye, a visible dye, a bioluminescent material, a chemiluminescent material, a radioactive material, or an enzymatic substrate.

113. The method of claim 112, wherein the bioluminescent material is green fluorescent protein (GFP) or red fluorescent protein (RFP).
114. The method of claim 112, wherein detection of the fluorescent dye or a visible dye is carried out by fluorometric or spectrophotometric measurement.
115. A method for identifying bioactivities or biomolecules produced by a cell comprising:
 - growing a mycelia-producing cell type under conditions and for a time sufficient to allow the cell to produce a bioactivity or biomolecule; and
 - screening for such bioactivities or biomolecules using a fluorescence analyzer.
116. The method of claim 115, wherein the mycelia-producing cell type is a recombinant cell.
117. The method of claim 115, wherein the mycelia-producing cell type is a non-recombinant cell.
118. The method of claim 115, wherein the biomolecule is a secondary metabolites.
119. The method of claim 117, wherein the cell is a *Streptomyces*.
120. The method of claim 119, wherein the *Streptomyces* is *Streptomyces venezuelae*.
121. The method of claim 115, wherein the cell is a filamentous bacteria or fungi.
122. The method of claim 115, wherein the growth conditions include liquid culture.

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